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Reduced glomerular filtration and enhanced bicarbonate reabsorption maintain metabolic alkalosis in humans

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Reduced glomerular filtration and enhanced bicarbonate reabsorption maintain metabolic alkalosis in humans. The mechanism that sustains chloride-depletion metabolic alkalosis is presumed to be a stimulation of renal acidification, so that the elevated filtered bicarbonate load that attends hyperbicarbonatemia is completely reabsorbed. However, such enhancement of renal bicarbonate reabsorption is not necessary to maintain hyperbicarbonatemia if the filtered bicarbonate load is not increased owing to a concomitant reduction in glomerular filtration rate (GFR). To assess the relative contributions of enhanced renal bicarbonate reabsorption and reduced GFR in the maintenance of chloride-depletion alkalosis in humans, selective hydrochloric acid depletion was induced in five normal subjects. Plasma bicarbonate concentration increased by 27% (25.3 ± 0.1 to 32.1 ± 0.3 mEq/liter, $P < 0.005$), whereas the rate of renal bicarbonate reabsorption increased by only 17% (2.7 ± 0.1 to 3.2 ± 0.2 mEq/min, $P < 0.05$) owing to a 10% reduction in GFR (93.2 ± 4.4 to 84.3 ± 4.1 ml/min, $P < 0.01$). Thus, in chloride-depletion metabolic alkalosis in humans, the increase in plasma bicarbonate concentration is not attended by a commensurate increase in filtered bicarbonate and rate of renal bicarbonate reabsorption. Both a reduction in GFR and an enhancement of renal bicarbonate reabsorption contribute to maintenance of the alkalotic state.

La diminution de la filtration glomérulaire et de la stimulation de la réabsorption des bicarbonates maintient de l'alcalose métabolique chez l'homme. Le mécanisme maintenant une alcalose métabolique par déplétion chlorurée est probablement une stimulation de l'acidification rénale de telle sorte que la charge filtrée élevée des bicarbonates qui accompagne l'hyperbicarbonatémie est complètement réabsorbée. Néanmoins, une telle stimulation de la réabsorption rénale des bicarbonates n'est pas nécessaire pour maintenir une hyperbicarbonatémie si la charge filtrée de bicarbonates n'est pas augmentée en raison d'une réduction concomitante du débit de filtration glomérulaire (GFR). Afin de préciser les contributions relatives de l'augmentation de la réabsorption rénale des bicarbonates et de la réduction de GFR dans le maintien de l'alcalose par déplétion en chlorures chez les hommes, une déplétion hydrochlorique sélective a été induite chez cinq sujets normaux. La bicarbonatémie s'est élevée de 27% (de 25,3 ± 0,1 à 32,1 ± 0,3 mEq/liter, $P < 0,005$ alors que le débit de réabsorption rénale de bicarbonates n'augmentait que de 17% (de 2,7 ± 0,1 à 3,2 ± 0,2 mEq/min, $P < 0,05$) en raison d'une réduction de 10% de GFR (de 93,2 ± 4,4 à 84,3 ± 4,1 ml/min, $P < 0,01$). Ainsi, lors d'une alcalose métabolique par déplétion chlorurée chez les hommes, l'élévation de la bicarbonatémie ne s'accompagne pas d'une augmentation identique des bicarbonates filtrés et du débit de réabsorption rénale des bicarbonates. A la fois la réduction de GFR et la stimulation de la réabsorption rénale des bicarbonates contribuent au maintien de l'état d'alcalose.

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For metabolic alkalosis to develop, a high blood bicarbonate concentration must first be generated by either hydrogen ion loss from the body (gastric or urine acid loss) or by exogenous base administration. The normal renal response to an increase in the plasma bicarbonate concentration of extra-renal origin is to develop bicarbonaturia, which spontaneously normalizes the blood acid-base status [1]. Thus, metabolic alkalosis may only persist if the kidney is "reset" so that all the filtered bicarbonate is reabsorbed despite hyperbicarbonatemia. This increase in the threshold for bicarbonate excretion by the kidney might occur because of two pathophysiologic mechanisms: *(1)* The glomerular filtration rate (GFR) may decrease as the plasma bicarbonate concentration increases so that, with the filtered bicarbonate load unchanged, a normal rate of renal bicarbonate reabsorption suffices to prevent bicarbonaturia. Alternatively, *(2)* as the plasma bicarbonate concentration rises, the GFR may remain unchanged so an increased rate of renal bicarbonate reabsorption prevents bicarbonaturia.

Recent studies from our laboratory showed that, in the rat, chronic metabolic alkalosis was maintained by the first pathophysiologic alternative given above. GFR was reduced while the filtered bicarbonate load and net renal bicarbonate reabsorption were unchanged [2]. In humans, there is conflicting data concerning the role of a reduction in GFR in maintaining metabolic alkalosis. GFR has been found to be decreased [3, 4], unchanged [5, 6], or even increased [7] during metabolic alkalosis.

The purpose of the present study was to re-examine the relative contributions of a reduction in GFR versus that of an increase in renal bicarbonate reabsorption in the maintenance of chronic metabolic alkalosis induced by gastric aspiration in humans.

Methods

Selective depletion of hydrochloric acid was performed to induce metabolic alkalosis in five healthy, nonsmoking male volunteers (ages 29 to 43) in a protocol modeled after that of Kassirer and Schwartz [5]. The composition of the low salt, whole food diet ingested for the entire study was (per kilogram of body weight): 43.7 kcal; 1.4 g protein; 0.15 mEq sodium; 0.88 mEq potassium; 3.4 mg calcium; 12.3 mg phosphorus; and 56 ml distilled water.

Study design. A pre-control period of 10 days was allowed to obtain steady-state values for plasma and urine acid-base and electrolyte composition. During the subsequent 4-day con-

trol period, daily afternoon sets of iothalamate clearances were performed and arterialized blood gases were obtained. Following completion of the control measurements, metabolic alkalosis was induced over the next 10 days. During this period, four to six gastric aspirations were performed by nasogastric or orogastric intubation. Each gastric aspiration lasted 4.5 hr. Pentagastrin 6 μg/kg s.c. was administered after insertion of the tube and at 90 and 180 min. Gastric aspiration was terminated if the plasma potassium level was less than 2.5 mEq/liter. At the end of the gastric aspiration period, the amount of sodium aspirated was returned (as sodium chloride) to each subject, and the volume was replaced with water. Gastric potassium loss was returned (as potassium chloride) to one subject who incurred a plasma potassium level of 2.17 mEq/liter. After postdrainage observation of at least 48 hr, iothalamate clearances were re-measured for 4 successive days as previously outlined.

General techniques. All studies were performed using standard balance techniques on the General Clinical Research Center of Moffitt Hospital, University of California, San Francisco, California. Approval was obtained from the institutional Committee on Human Research and informed consent was obtained from each subject. Balance techniques and analytical methods used in this laboratory have been reported previously [7].

Clearance techniques. A water diuresis was established and baseline collections of urine and plasma were obtained 2.5 hr after lunch. A loading dose of 0.107 ml/kg body weight of meglumine iothalamate (Conray 60) was administered intravenously followed by a maintenance infusion to achieve a meglumine iodine level of approximately 15 mg/dl. After a 1-hr equilibration period, sequential 30-min urine collections commenced. Plasma samples were obtained at the midpoint of each urine collection. Each subject remained supine except to urinate. Two arterialized blood samples were obtained during the clearance periods for estimation of arterial pH, P_{CO_2}, and total CO_2. The first two clearance periods were discarded since a steady-state was not reached in most subjects and the next three collection periods of each day were used to calculate iothalamate clearance.

Measurements and calculations. Arterialized venous blood gas determinations were obtained after the hand had been immersed in a 44°C water bath for 10 min [7]. Plasma bicarbonate concentration and carbon dioxide tension were calculated using the Henderson-Hasselbalch equation from the measured values of blood pH (Radiometer BMS-3 pH electrode, Westlake, Ohio) and plasma total carbon dioxide (Ericsen CO_2 analyzer, Ossining, New York) using a pK'_a of 6.1 and a carbon dioxide solubility coefficient of 0.0301. Iothalamate was measured by the fluorescent excitation technique [8]. Plasma water iothalamate concentration was corrected for an effective "Donnan factor" across the glomerular capillary wall of 1.05 in the control period [9] and 1.06 in the alkalotic period [2]. GFR during the study period was estimated as the clearance of iothalamate and was normalized to 1.73 m^2 body surface area. Filtered bicarbonate load was the product of the ultrafiltrable arterial bicarbonate concentration (also corrected for plasma solids and a Donnan factor) and the GFR. Net renal acidification (or hydrogen ion secretion) was calculated as the filtered bicarbonate load plus urinary net acid excretion (ammonium plus titratable acid minus bicarbonate).

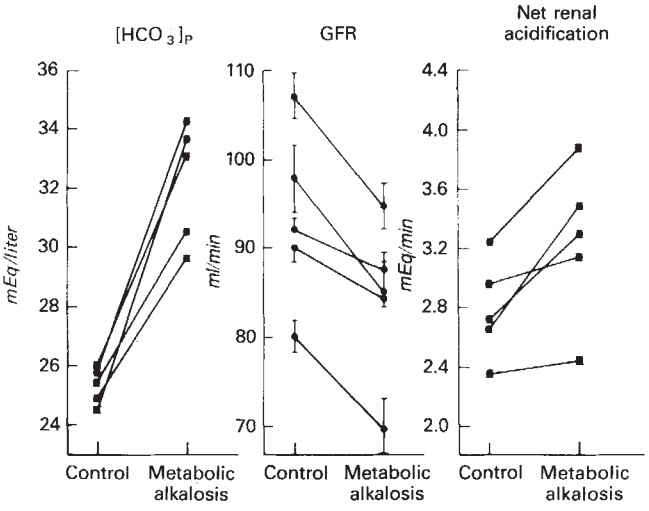

Fig. 1. *Mean changes in plasma bicarbonate concentration ($[HCO_3^-]_P$), GFR, and net renal acidification for each of the five subjects in the 4-day control and the metabolic alkalosis periods.*

Statistical analysis. All values are expressed as mean ± SEM. Significance was assessed by the paired Student's *t* test.

Results

Gastric aspiration was successful in inducing metabolic alkalosis: There were increases in arterial pH from 7.41 ± 0.002 to 7.48 ± 0.003; in P_{CO_2} from 41.0 ± 0.4 to 43.9 ± 0.4 mm Hg; and in bicarbonate concentration from 25.3 ± 0.1 to 32.1 ± 0.3 mEq/liter ($P < 0.005$). Potassium deficiency occurred as evidenced by a fall in plasma potassium from 3.63 ± 0.03 to 2.62 ± 0.04 mEq/liter ($P < 0.001$) and by a cumulative negative potassium balance of 254 ± 47 mEq. Negative chloride balance of 282 ± 43 mEq was induced. Weight loss was 0.7 ± 0.3 kg ($P < 0.05$).

Accompanying the 27% rise in plasma bicarbonate concentration was a fall in GFR in each subject. GFR fell by 10%, from 93.2 ± 4.4 to 84.3 ± 4.1 ml/min ($P < 0.01$), as shown in Figure 1. Within each period, GFR did not vary significantly from day to day for each individual. Since the fractional changes in GFR and plasma bicarbonate concentration were not of the same magnitude, the calculated filtered bicarbonate load rose by 17%, from 2.7 ± 0.1 to 3.2 ± 0.2 mEq/min ($P < 0.05$). Bicarbonaturia in each period was negligible and urinary net acid excretion for each subject was similar in each period (0.91 ± 0.04 mEq/kg/day), so that both renal bicarbonate reabsorption and net renal hydrogen ion secretion were also increased by 17%, as shown in Figure 1.

Discussion

The important finding in this study of chloride-depletion metabolic alkalosis in humans was that the alkalosis was associated with a reduction in GFR and an increase in renal bicarbonate reabsorption. The required increase in renal bicarbonate reabsorption was only 60% of that which would have been necessary to maintain the same degree of alkalosis if GFR had not changed. Put another way, if the responsibility for

maintaining metabolic alkalosis is divided between a reduction in GFR and enhanced renal bicarbonate reabsorption, the contribution of the former was 40% while that of the latter was 60%.

This study does not define whether a similar fall in GFR and rise in bicarbonate reabsorption occur in other forms of metabolic alkalosis or in more severe examples of alkalosis. Furthermore, these studies do not establish whether a fall in GFR is essential for the maintenance of metabolic alkalosis (that is, if GFR had remained normal, whether a sufficient increment in bicarbonate reabsorption could have occurred to sustain the same degree of hyperbicarbonatemia as was observed in the present studies). Nevertheless, the results show that a reduction in GFR and an increase in renal bicarbonate reabsorption have the potential of participating jointly in the maintenance of chronic metabolic alkalosis.

The degree of alkalosis achieved in our study was comparable to that of Kassirer and Schwartz [5]; they, however, did not detect a fall in GFR. In the present study, the observed 10% reduction in GFR was demonstrated by a paired comparison of a set of 12 clearances in both periods in each of five patients. Details of the protocol used to measure GFR in the two patients studied by Kassirer and Schwartz were not given [5]. It is therefore not clear whether or not their protocol was sufficiently sensitive to detect small changes in GFR.

Previous micropuncture and clearance studies shed some light on how the chloride and potassium deficiencies and hypermineralocorticoidism accompanying this form of gastric alkalosis might mediate the reduction in GFR and stimulation of proximal and/or distal tubular bicarbonate reabsorption. If extracellular volume depletion accompanies chloride depletion, there might be a reduction in renal blood flow and hence GFR [10]. There is little evidence that extracellular volume contraction has much of an effect on absolute proximal bicarbonate reabsorption [11]. But, by stimulating renin and hence aldosterone, volume contraction may increase distal acidification. This enhancement of distal acidification may be offset, however, by a simultaneous reduction in other determinants of distal H^+ secretion, notably sodium delivery and flow rate.

While potassium depletion has been suggested to be merely a by-product of induction of the alkalotic state [12], it has also been suggested that potassium depletion helps maintain the alkalosis [2, 7]. For instance, potassium depletion has been shown to decrease GFR in animals [2, 13, 14] by inducing vasoconstriction due to angiotensin and thromboxane release [15]. A role for altered tubuloglomerular feedback to reduce GFR during potassium deficiency may also be possible [16]. Whether such hemodynamic effects occur in humans with pure potassium deficiency is unknown. Although it remains controversial whether or not potassium depletion increases proximal bicarbonate reabsorption [2, 17, 18], it has been demonstrated in dogs that potassium depletion is synergistic with aldosterone in stimulating distal acidification [19].

In addition, a small increment in renal bicarbonate reabsorption may be ascribed to the secondary chronic hypercapnia [20].

In summary, in this clinical model of chronic metabolic alkalosis secondary to gastric aspiration, the alkalotic state was maintained by a combination of a reduction in GFR and an augmentation of tubular bicarbonate reabsorption. Whether the relative contributions to the maintenance of the alkalotic state by a reduction in GFR (40%) and increase in tubular transport (60%) remain similar with other causes of metabolic alkalosis [7, 19] and with more severe degrees of alkalosis awaits definition. Chloride and/or potassium depletion are potentially capable of inducing the changes in renal hemodynamics and tubular acidification necessary to sustain metabolic alkalosis.

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